IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANT: James P. Elia)
)
SERIAL NO.: 09/064,000) EXAMINER: Nicholas D. Lucchesi
)
FILED: April 21, 1998)
) GROUP ART UNIT: 3732
FOR: METHOD AND APPARATUS)
FOR INSTALLATION OF)
DENTAL IMPLANT)

DECLARATION OF G. ROBERT MEGER, M.D.

I G. Robert Meger declare as follows:

1. I have offices at 3333 East Camelback Road, Phoenix, Arizona 85018.

2. My Curriculum Vitae is attached hereto as Exhibit A.

3. I have read and understood the disclosures at column 14, lines 4-61 and column 21, lines 1-26 of United States Patent Number 5,397,235 (hereinafter " '235 patent") entitled "Method for Installation of Dental Implant," and granted to James P. Elia on March 14, 1995. A copy of such disclosures is attached hereto as Exhibit B. I understand that the same disclosures are contained in above patent Application Serial No. 09/064,000.

4. I note that the disclosures mentioned in above Paragraph 3 relate to a method for forming a bud and resulting soft tissue. Such methods involve placing a growth factor at a desired site of a body with use of techniques including resorbable and non-resorbable carriers, gels, time-release capsules, and granules. In addition, the growth factor may be placed in the body orally, systemically, by injection.

through the respiratory tract, by making an incision in the body and then inserting the growth factor. I note further that the growth factor and/or carrier may be activated by tissue pH, enzymes, ultrasound, electricity, heat, or in vivo chemicals.

5. The materials included in Exhibit C of this Declaration illustrate that the techniques set forth in above Paragraph 4 were well known to those skilled in the medical arts prior to July 2, 1993. It is my opinion that one skilled in the medical arts armed with such knowledge would have been able to practice the invention(s) described at column 14, lines 4-61 and column 21, lines 1-26 of the '235 patent without need for resorting to undue experimentation.

6. Declarant states that the above opinion was reached independently.

Declarant understands that (1) any willful false statements and the like made herein are punishable by fine or imprisonment, or both (18 U.S.C. 1001) and may jeopardize the validity of the application or any patent issuing thereon, and (2) that all statements made of Declarant's own knowledge are true and that all statements made on information and belief are believed to be true.

Further Declarant sayeth not.

Date: 2/13/01

G. Robert Meger

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EXHIBIT A

CURRICULUM VITAE

CURRICULUM VITAE

G. Robert Meger, M.D.

Birthplace:	Cedar Rapids, Iowa
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Board Certifications:	American Board of Plastic Surgery American Board of Surgery
Memberships:	American Society of Plastic Surgeons Maricopa County Society of Plastic Surgeons American Medical Association
License:	Board of Medical Examiners State of Arizona #23447
Residency:	Plastic Surgery Medical College of Georgia Augusta, Georgia

General Surgery
Phoenix Integrated Surgical Residency
Good Samaritan Regional Medical Center
Phoenix, Arizona

Surgical Internship
Maricopa Medical Center
Phoenix, Arizona

Education:

Doctor of Medicine
Creighton University
Omaha, Nebraska

Bachelor of Science in Chemistry
University of Notre Dame
Notre Dame, Indiana

EXHIBIT
B

DISCLOSURES

Growth factors can be utilized to induce the growth of "hard tissue" or bone and "soft tissues" like ectodermal and mesodermal tissues. As used herein, the term growth factor encompasses compositions and living organisms which promote the growth of hard tissue, such as bone, or soft tissue in the body of a patient. The compositions include organic and inorganic matter. The compositions can be genetically produced or manipulated. The living organisms can be bacteria, viruses, or any other living organism which promote tissue growth. By way of example and not limitation, growth factors can include platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (acidic/basic)(FGF a,b), interleukins (IL's), tumor necrosis factor (TNF), transforming growth factor (TGF-B), colony-stimulating factor (CSF), osteopontin (Eta-1 (OPN), platelet-derived growth factor (PDGF), interferon (INF), bone morphogenic protein 1 (BMP-1), and insulin growth factor (IGF). Recombinant and non-recombinant growth factors can be utilized as desired. Bacteria or viruses can, when appropriate, be utilized as growth factors. For example, there is a bacterial hydrophilic polypeptide that self-assembles into a nanometer internal diameter pore to build a selective lipid body. Various enzymes can be utilized for the synthesis of peptides which contain amino acids that control three-dimensional protein structure and growth. Growth factors can be applied in gels or other carriers which regulate the rate of release of the growth factors and help maintain the growth factors, and the carrier, at a desired location in the body. Time release capsules, granules, or other carriers containing growth factor can be activated by tissue pH, by enzymes, by ultrasound, by electricity, by heat, by selected in vivo chemicals or by any other selected means to release the growth factor. The carrier can be resorbable or non-resorbable. Or, the growth factor itself can be activated by similar means. Either the carrier or the growth factor can mimic extracellular fluid to control cell growth, migration, and function. The growth factor can be administered orally, systemically, in a carrier, by hypodermic needle, through the respiratory tract, or by any other desired method. The growth factor can also be administered into a capsule or other man-made composition or structure placed in the body. While administration of the growth factor is presently usually localized in the patient's body, circumstances may arise where it is advantageous to distribute a growth factor throughout the patient's body in uniform or non-uniform concentrations. An advantage to growth factors is that they can often, especially when in capsule form or in some other containment system, be inserted to a desired site in the body by simply making a small incision and inserting the growth factor. The making of such a small incision comprises minor surgery which can often be accomplished on an out-patient basis. The growth factors can be multifactorial and nonspecific.

In another embodiment of the invention, genetically produced living material is used to form an implant in the bone of a patient. The DNA structure of a patient is analyzed from a sample of blood or other material extracted from a patient and a biocompatible tooth bud **122** (FIG. 3) is produced. The bud **122** is placed in an opening **123** in the alveolar bone and packing material is placed around or on top of the bud **122**. The size of opening **123** can vary as desired. The packing around bud **122** can comprise HAC **124**, hydroxyapatite, blood, growth factors, or any other desirable packing material. The bud **122** grows into a full grown tooth in the same manner that tooth buds which are in the jaws of children beneath baby teeth grow into full sized teeth. Instead of bud **122**, a quantity of genetically produced living material which causes bud **122** to form in the alveolar bone can be placed at a desired position in the alveolar bone such that bud **122** forms and grows into a full sized tooth. Instead of forming an opening **123**, a needle or other means can be used to simply inject the genetically produced living material into a selected location in the alveolar bone. As would be appreciated by those skilled in the art, genetically produced materials can be inserted in the body to cause the body to grow, reproduce, and replace leg bone, facial bone, and any other desired soft and hard tissue in the body.

EXHIBIT C

EXHIBIT C
SUMMARY OF MATERIALS

TECHNIQUES OF INTRODUCING
AND ACTIVATION OF GROWTH FACTORS

EXH. NO.	MATERIAL AND DATE	TECHNIQUE
C-1	J Periodontal, November 1991, "Effects of platelet-derived growth fctor/insulin-like growth factor-1 combination on bone regeneration around titanium dental implants". Lynch S.E., et. al.	Gel carrier
C-2	Nature, November 28, 1991, "Electrically erodible polymer gel for controlled release of drugs". Kwon, I.C., et. al.	Possibility of multiple chemical release stimuli of gel for controlled release
C-3	Acta Orthop Scand, October 1991, "Dose-dependent stimulation of bone induction by basic fibroblast growth in rats". Aspenberg P., et. al.	Gel carrier
C-4	Natl. Acad. Sci., November 1992, "Heat shock induces the release of fibroblast growth factor 1 from NIH 3T3 cells". Jackson A., et. al.	Heat activation of growth factor
C-5	Transplant, 1992, "Cell transplantation for myocardial repair: an experimental approach". Marelli D., et. al.	Heart injection
C-6	Lasers Sur. Med., 1989, "Macrophage responsiveness to light therapy". Young, S.	Light activation
C-7	J Surg. Res., May 1989, "Attachment of peptide growth factors to implantable collagen". Stompro B.E., et. al.	Absorbable carrier
C-8	Clin. Orthop., February 1991, "Bone morphogenesis of rabbit bone morphogenetic protein-bound hydroxyapatite-fibrin composite". Sato T., et. al.	Non-absorbable carrier
C-9	Arch Surg., June 1989, "Angiotropin treatment prevents flap necrosis and enhances dermal regeneration in rabbits". Hockel M., Burke J.F.	Injection

EXH. NO.	MATERIAL AND DATE	TECHNIQUE
C-10	JAMA, October, 1991, "Tissue transformation into bone in vivo. A potential practical application". Khouri R.K., et. al.	Injection
C-11	Radiology, December 1986, "An experimental evaluation of microcapsules for arterial chemoembolilzation". Bechtel W., et. al.	Intra Arterial capsule delivery
C-12	Atherosclerosis, February 1989, "Histopathologic examination of material from angioplasty balloon catheters used in vivo in human coronary arteries". Sprecher D.L., et. al.	Coronary heart catheter
C-13	Int. J Cancer, May 1989, "Acidic Cellular Environments: activation of latent TGF-beta and sensitization of cellular responses to TGF-beta and EGF". Dullien P., et. al.	pH activation
C-14	Atherosclerosis, April 1990, "Endothelial cell stimulation of smooth muscle glycosamino-glycan sythesis can be accounted for by transforming growth factor beta activity". Merrilees M.J., Scott L.	Heat activation
C-15	Ultrasound Med Biol, 1990, "Macrophage responsiveness to therapeutic ultrasound". Young S.R., Dyson M.	Ultrasound activation
C-16	Am J Physiol, September 1989, "Mitogenic signals for thrombin in mesangial cells: regulation of phosspholipase C and PDGF genes". Schultz P.J., et. al.	Enzyme activation
C-17	J Burn Cure Rehabil, July-August, 1991, "Weak direct current accelerates split-thickness healing on tangentially excised second-degree burns". Chu C.S., et. al.	Electrical activation

List Contains 1 Item.
Current Search Formulation: +LYNCH SE; + 1991 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Effects of the platelet-derived growth factor/insulin-like growth factor-I combination on bone regeneration around titanium dental implants. Results of a pilot study in beagle dogs.
ARTICLE SOURCE: J Periodontol (United States), Nov 1991, 62(11) p710-6
AUTHOR(S): Lynch SE; Buser D; Hernandez RA; Weber HP; Stich H; Fox CH; Williams RC
AUTHOR'S ADDRESS: Department of Periodontology, Harvard School of Dental Medicine, Boston, MA
MAJOR SUBJECT HEADING(S): Bone Regeneration [drug effects]; Dental Implantation, Endosseous; Dental Implants; Insulin-Like Growth Factor I [therapeutic use]; Mandible [surgery]; Platelet-Derived Growth Factor [therapeutic use]; Titanium
MINOR SUBJECT HEADING(S): Analysis of Variance; Dogs; Drug Combinations; Gels; Insulin-Like Growth Factor I [administration & dosage]; Mandible [pathology] [physiopathology]; Methylcellulose; Pilot Projects; Placebos; Platelet-Derived Growth Factor [administration & dosage]; Recombinant Proteins; Wound Healing
INDEXING CHECK TAG(S): Animal; Female; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: The purpose of this study was to evaluate the early wound healing events of bone around press-fit titanium implants inserted with and without the concurrent application of a combination of platelet-derived growth factor (PDGF) and insulin-like growth factor (IGF-I). Nine months prior to implant placement all mandibular premolar teeth were extracted in 8 beagle dogs. Subsequently, 40 specially manufactured titanium implants with 2 transverse holes in the apical section were press fit into precise recipient sites in the dogs' mandibles. The dogs were sacrificed at 7 and 21 days following implant placement yielding 12 PDGF-B/IGF-I treated and 8 control (placebo gel or non-treated) implants for each observation period. Coded undecalcified sections were analyzed for: 1) percentage of implant surface in contact with new bone; 2) percentage of peri-implant space filled with new bone; and 3) percentage of implant hole filled with new bone. An analysis of variance was used to determine significant differences among the treatment groups. At 7 days, the percentage of bone fill in the peri-implant spaces and the percentage of implant surface in contact with new bone were both significantly increased in PDGF-B/IGF-I treated sites (P less than 0.01 for both groups). There was less than 1.5% fill of the implant holes in both treated and control sites (no significant differences). At 21 days the percentage of bone fill in the peri-implant spaces was significantly increased in the PDGF-B/IGF-I treated sites (P less than 0.01).(ABSTRACT TRUNCATED AT 250 WORDS).
MEDLINE INDEXING DATE: 199204
ISSN: 0022-3492
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 92092155
CAS REGISTRY/EC NUMBER(S): 0 (Dental Implants); 0 (Drug Combinations); 0 (Gels); 0 (Placebos); 0 (Platelet-Derived Growth Factor); 0 (Recombinant Proteins); 67763-96-6 (Insulin-Like Growth Factor I); 7440-32-6 (Titanium); 9004-67-5 (Methylcellulose)
GRANT ID NUMBER: 5T32 DE07010-DE-NIDR; K16 DE 0027501-DE-NIDR

EXHIBIT C-1

List Contains 1 Item.
Current Search Formulation: "gel delivery"

This Document Selected From: 1986 - 1995 SurgAnLine® [1996 Edition]

ARTICLE TITLE: Electrically erodible polymer gel for controlled release of drugs.
ARTICLE SOURCE: Nature (England), Nov 28 1991, 354(6351) p291-3
AUTHOR(S): Kwon IC; Bae YH; Kim SW
AUTHOR'S ADDRESS: Center for Controlled Chemical Delivery, University of Utah, Salt Lake City 84108.
MAJOR SUBJECT HEADING(S): Delayed-Action Preparations
MINOR SUBJECT HEADING(S): Acrylic Resins [chemistry]; Electric Stimulation; Hydrogen-Ion Concentration; Insulin [administration & dosage]; Oxazoles [chemistry]; Polymers [chemistry]; Polymethacrylic Acids [chemistry]; Solubility
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: New controlled drug-delivery systems are being explored to overcome the disadvantages of conventional dosage forms. For example, stimulated drug-delivery has been used to overcome the tolerance problems that occur with a constant delivery rate, to mimic the physiological pattern of hormonal concentration and to supply drugs on demand. Stimuli-sensitive polymers, which are potentially useful for pulsed drug delivery, experience changes in either their structure or their chemical properties in response to changes in environmental conditions. Environmental stimuli include temperature, pH, light (ultraviolet or visible), electric field or certain chemicals. Volume changes of stimuli-sensitive gel networks are particularly responsive to external stimuli, but swelling is slow to occur. As well as being useful in the controlled release of drugs, such systems also provide insight into intermolecular interactions. Here we report on a novel polymeric system, which rapidly changes from a solid state to solution in response to small electric currents, by disintegration of the solid polymer complex into two water-soluble polymers. We show that the modulated release of insulin, and by extension other macromolecules, can be achieved with this polymeric system.
MEDLINE INDEXING DATE: 9203
ISSN: 0028-0836
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 92065953
CAS REGISTRY/EC NUMBER(S): 0 (Acrylic Resins); 0 (Delayed-Action Preparations); 0 (Oxazoles); 0 (Polymers); 0 (Polymethacrylic Acids); 11061-68-0 (Insulin); 25087-26-7 (polymethacrylic acid); 25805-17-8 (polyethyloxazoline); 9003-01-4 (carbopol 940)

EXHIBIT C-2

List Contains 1 Item.
Current Search Formulation: +ASPENBERG P; + 1991 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Dose-dependent stimulation of bone induction by basic fibroblast growth factor in rats.
ARTICLE SOURCE: Acta Orthop Scand (Denmark), Oct 1991, 62(5) p481-4
AUTHOR(S): Aspenberg P; Thorngren KG; Lohmander LS
AUTHOR'S ADDRESS: Lund University Hospital Department of Orthopedics, Sweden.
MAJOR SUBJECT HEADING(S): Bone Matrix [transplantation]; Fibroblast Growth Factor, Basic [pharmacology]; Osteogenesis [drug effects]
MINOR SUBJECT HEADING(S): Abdominal Muscles [surgery]; Bone Matrix [chemistry]; Calcium [analysis]; Dose-Response Relationship, Drug; Fibroblast Growth Factor, Basic [administration & dosage]; Rats, Inbred Strains; Rats
INDEXING CHECK TAG(S): Animal; Female; Support, Non-U.S. Gov't
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Implantation of demineralized bone matrix in rodents elicits a series of cellular events leading to the formation of new bone inside and adjacent to the implant. This process is believed to be initiated by an inductive protein present in bone matrix, and local growth factors may further regulate the process. We have previously shown that local application of recombinant human basic fibroblast growth factor (bFGF) in a carboxymethyl cellulose gel to demineralized bone matrix implants increases the bone yield as measured by calcium content 3 weeks after implantation in rats. We now report that this increase was seen at 3 and 4 weeks, but not earlier or later. Further, the stimulatory effect was seen with doses from 3 to 75 ng per implant. A dose of 0.6 or 380 ng did not increase the bone yield, and 1,900 ng had a marked inhibitory effect. This narrow dosage optimum may reflect the complex actions of the growth factor.
MEDLINE INDEXING DATE: 199202
ISSN: 0001-6470
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 92057648
CAS REGISTRY/EC NUMBER(S): 0 (Fibroblast Growth Factor, Basic); 7440-70-2 (Calcium)

EXHIBIT C-3

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Selected full citations from 114 MEDLINE records

✔ Related Articles External Links

TITLE: Heat shock induces the release of fibroblast growth factor 1 from NIH 3T3 cells.

AUTHORS: Jackson A; Friedman S; Zhan X; Engleka KA; Forough R; Maciag T

AUTHOR AFFILIATION: Department of Molecular Biology, Jerome H. Holland Laboratory for the Biomedical Sciences, American Red Cross, Rockville, MD 20855.

SOURCE: Proc Natl Acad Sci U S A 1992 Nov 15;89(22):10691-5

CITATION IDS: PMID: 1279690 UI: 93066309

ABSTRACT: Fibroblast growth factor 1 (FGF-1) is a potent angiogenic and neurotrophic factor whose structure lacks a classical signal sequence for secretion. Although the initiation of these biological activities involves the interaction between FGF-1 and cell surface receptors, the mechanism responsible for the regulation of FGF-1 secretion is unknown. We report that murine NIH 3T3 cells transfected with a synthetic gene encoding FGF-1 secrete FGF-1 into their conditioned medium in response to heat shock. The form of FGF-1 released by NIH 3T3 cells in response to increased temperature (42 degrees C, 2 hr) in vitro is not biologically active and does not associate with either heparin or the extracellular NIH 3T3 monolayer matrix. However, it was possible to derive biologically active FGF-1 from the conditioned medium of heat-shocked NIH 3T3 cell transfectants by ammonium sulfate fractionation. The form of FGF-1 exposed by ammonium sulfate fractionation is similar in size to cytosolic FGF-1 and can bind and be eluted from immobilized heparin similarly to the recombinant human FGF-1 polypeptide. Further, the release of FGF-1 by NIH 3T3 cell transfectants in response to heat shock is reduced significantly by both actinomycin D and cycloheximide. These data indicate that increased temperature may upregulate the expression of a factor responsible for the secretion of FGF-1 as a biologically

EXHIBIT C-4

inactive complex that requires an activation step to exhibit the biological activity of the extracellular polypeptide mitogen.

MAIN MESH HEADINGS:
Fibroblast Growth Factor, Acidic/*biosynthesis
*Heat

ADDITIONAL MESH HEADINGS:
Animal
Cell Division
Culture Media, Conditioned
Cycloheximide/pharmacology
Cytosol/metabolism
Dactinomycin/pharmacology
DNA/biosynthesis
Fibroblast Growth Factor, Acidic/genetics
Fibroblast Growth Factor, Acidic/pharmacology
Fibroblast Growth Factor, Acidic/secretion
Genes, Synthetic
Immunoblotting
Kinetics
Mice
Recombinant Proteins/pharmacology
Support, U.S. Gov't, P.H.S.
Thymidine/metabolism
Transfection
Tritium
3T3 Cells
1992/11
1992/15 00:00

PUBLICATION TYPES:
JOURNAL ARTICLE

CAS REGISTRY NUMBERS:
0 (Culture Media, Conditioned)
0 (Recombinant Proteins)
10028-17-8 (Tritium)
104781-85-3 (Fibroblast Growth Factor, Acidic)
50-76-0 (Dactinomycin)
50-89-5 (Thymidine)
66-81-9 (Cycloheximide)
9007-49-2 (DNA)

LANGUAGES:
Eng

GRANT/CONTRACT ID:
HL32348/HL/NHLBI
HL44336/HL/NHLBI

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List Contains 1 Item.
Current Search Formulation: +MARELLI D

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Cell transplantation for myocardial repair: an experimental approach.
ARTICLE SOURCE: Cell Transplant (United States), 1992, 1(6) p383-90
AUTHOR(S): Marelli D; Desrosiers C; el-Alfy M; Kao RL; Chiu RC
AUTHOR'S ADDRESS: Department of Surgery, McGill University, Montreal, Quebec, Canada.
MAJOR SUBJECT HEADING(S): Muscles [transplantation]; Myocardial Diseases [surgery]; Myocardium [pathology]; Transplantation, Heterotopic
MINOR SUBJECT HEADING(S): Cells, Cultured; Dogs; Freezing; Muscles [cytology] [physiology]; Myocardial Diseases [pathology]; Regeneration; Tissue Culture [methods]; Transplantation, Autologous; Transplantation, Heterotopic [methods] [physiology]
INDEXING CHECK TAG(S): Animal; Support, Non-U.S. Gov't
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Myocardium lacks the ability to regenerate following injury. This is in contrast to skeletal muscle (SKM), in which capacity for tissue repair is attributed to the presence of satellite cells. It was hypothesized that SKM satellite cells multiplied in vitro could be used to repair injured heart muscle. Fourteen dogs underwent explantation of the anterior tibialis muscle. Satellite cells were multiplied in vitro and their nuclei were labeled with tritiated thymidine 24 h prior to implantation. The same dogs were then subjected successfully to a myocardial injury by the application of a cryoprobe. The cells were suspended in serum-free growth medium and autotransplanted within the damaged muscle. Medium without cells was injected into an adjacent site to serve as a control. Endpoints comprised histology using standard stains as well as Masson trichrome (specific for connective tissue), and radioautography. In five dogs, satellite cell isolation, culture, and implantation were technically satisfactory. In three implanted dogs, specimens were taken within 6-8 wk. There were persistence of the implantation channels in the experimental sites when compared to the controls. Macroscopically, muscle tissue completely surrounded by scar tissue could be seen. Masson trichrome staining showed homogeneous scar in the control site, but not in the test site where a patch of muscle fibres containing intercalated discs (characteristic of myocardial tissue) was observed. In two other dogs, specimens were taken at 14 wk postimplantation. Muscle tissue could not be found. These preliminary results could be consistent with the hypothesis that SKM satellite cells can form neo-myocardium within an appropriate environment. Our specimens failed to demonstrate the presence of myocyte nuclei.(ABSTRACT TRUNCATED AT 250 WORDS).
MEDLINE INDEXING DATE: 199407
ISSN: 0963-6897
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 94199205

EXHIBIT C-5

List Contains 1 Item.
Current Search Formulation: +YOUNG S; + 1989 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Macrophage responsiveness to light therapy.
ARTICLE SOURCE: Lasers Surg Med (United States), 1989, 9(5) p497-505
AUTHOR(S): Young S; Bolton P; Dyson M; Harvey W; Diamantopoulos C
AUTHOR'S ADDRESS: Anatomy Department, United Medical School, Guy's Hospital, London, England
MAJOR SUBJECT HEADING(S): Growth Substances [physiology]; Lasers [therapeutic use]; Macrophages [radiation effects], Wound Healing [radiation effects]
MINOR SUBJECT HEADING(S): Cell Division [radiation effects]; Cell Line; Cells, Cultured; Fibroblasts [cytology] [radiation effects]; Growth Substances [secretion]; Kidney [cytology]; Macrophages [cytology] [secretion]; Mice
INDEXING CHECK TAG(S): Animal; Comparative Study; In Vitro; Support, Non-U.S. Gov't
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Macrophages are a source of many important mediators of wound repair. It was the purpose of this study to see if light could stimulate the release of these mediators. In this study an established macrophage-like cell line (U-937) was used. The cells were exposed in culture to the following wavelengths of light: 660 nm, 820 nm, 870 nm, and 880 nm. The 820-nm source was coherent and polarised, and the others were non-coherent. Twelve hours after exposure the macrophage supernatant was removed and placed on 3T3 fibroblast cultures. Fibroblast proliferation was assessed over a 5-day period. The results showed that 660-nm, 820-nm, and 870-nm wavelengths encouraged the macrophages to release factors that stimulated fibroblast proliferation above the control levels, whereas the 880-nm wavelength either inhibited the release of these factors or encouraged the release of some inhibitory factors of fibroblast proliferation. These results suggest that light at certain wavelengths may be a useful therapeutic agent by providing a means of either stimulating or inhibiting fibroblast proliferation where necessary. At certain wavelengths coherence is not essential.
MEDLINE INDEXING DATE: 199002
ISSN: 0196-8092
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 90042969
CAS REGISTRY/EC NUMBER(S): 0 (Growth Substances)

EXHIBIT C-6

List Contains 1 Item.
Current Search Formulation: +STOMPRO BE; + 1989 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Attachment of peptide growth factors to implantable collagen.
ARTICLE SOURCE: J Surg Res (United States), May 1989, 46(5) p413-21
AUTHOR(S): Stompro BE; Hansbrough JF; Boyce ST
AUTHOR'S ADDRESS: Department of Surgery, University of California, San Diego Medical Center 92103.
MAJOR SUBJECT HEADING(S): Collagen; Epidermal Growth Factor-Urogastrone; Epidermis [cytology]; Growth Substances; Heparin; Keratin
MINOR SUBJECT HEADING(S): Cell Division; Cells, Cultured; Drug Combinations; Epidermal Growth Factor-Urogastrone [pharmacology]; Growth Substances [pharmacology]; Heparin [pharmacology]; Wound Healing
INDEXING CHECK TAG(S): Support, U.S. Gov't, P.H.S.
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Ingrowth of fibrovascular tissue from the woundbed into collagen-based dermal substitutes and survival of cultured epithelium after transplantation may be enhanced by attachment of heparin binding growth factor 2 (HBGF2) and epidermal growth factor (EGF) to collagen. Biotinylation of collagen and the growth factors allows immobilization of HBGF2 and EGF by high affinity binding of tetravalent avidin. Biotinylated HBGF2 and EGF (B-GF) were exposed to complexes of biotinylated collagen (B-COL)-avidin (A) and detected with peroxidase-labeled avidin (AP) followed by chromagen formation on nitrocellulose paper. Binding of biotinylated HBGF2 and EGF was specific (*, P less than 0.05), proportional to the concentration of biotinylated collagen, and resistant to ionic (NaCl) displacement. Data are expressed as mean percentages of maximum binding +/- SEMs: (table; see text) Growth response of cultured human epidermal keratinocytes to HBGF2 (population doubling time, PDT = 0.70 population doublings (PD)/day) confirmed the retention of mitogenic activity after biotinylation (PDT = 0.80 PD/day). Specific binding of biotinylated HBGF2, EGF, or other biologically active molecules (antibiotics, NSAIDs) to implantable collagen may provide a mechanism for positive therapeutic modulation of wound healing, including repair of full-thickness skin wounds with cultured cell-collagen composite grafts.
MEDLINE INDEXING DATE: 198908
ISSN: 0022-4804
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 89237142
CAS REGISTRY/EC NUMBER(S): 0 (Drug Combinations); 0 (Fibroblast Growth Factor, Basic); 0 (Growth Substances); 62229-50-9 (Epidermal Growth Factor-Urogastrone); 68238-35-7 (Keratin); 9005-49-6 (Heparin); 9007-34-5 (Collagen)
GRANT ID NUMBER: GM35068-GM-NIGMS

EXHIBIT C-7

List Contains 1 Item.
Current Search Formulation: +SATO T; + 1991 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Bone morphogenesis of rabbit bone morphogenetic protein-bound hydroxyapatite-fibrin composite.
ARTICLE SOURCE: Clin Orthop (United States), Feb 1991, (263) p254-62
AUTHOR(S): Sato T; Kawamura M; Sato K; Iwata H; Miura T
AUTHOR'S ADDRESS: Department of Orthopaedic Surgery, Nagoya University School of Medicine, Japan.
MAJOR SUBJECT HEADING(S): Composite Resins [therapeutic use]; Fibrin [therapeutic use]; Growth Substances [therapeutic use]; Osteogenesis [drug effects]; Proteins [therapeutic use]
MINOR SUBJECT HEADING(S): Bone and Bones [drug effects]; Composite Resins [pharmacology]; Fibrin [pharmacology]; Growth Substances [pharmacology]; Hydroxyapatites [therapeutic use]; Proteins [pharmacology]; Rabbits
INDEXING CHECK TAG(S): Animal
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Hydroxyapatite (HAP) and fibrin have been implanted in patients and observed to be well tolerated in orthotopic sites. This is a report on a composite of HAP, fibrin, and rabbit bone morphogenetic protein and insoluble noncollagenous protein (BMP-iNCP). Drill holes in the femoral condyles of rabbits were packed with granulated HAP (200 mg), fibrin (0.3 ml), BMP-iNCP (5 mg), or various combinations of the two. The fibrin consisted mainly of sterilized human fibrinogen and thrombin, and BMP-iNCP was prepared from demineralized rabbit cortical bone. New bone formation was observed at one, two, four, and eight weeks after implantation. The BMP-iNCP augmented new bone formation in rabbit femoral condyles. Fibrin made the composite easier to manipulate and did not inhibit osteogenesis at any period. The composites of HAP with BMP-iNCP and of HAP with BMP-iNCP and fibrin produced higher yields of new bone than fibrin alone or HAP alone.
MEDLINE INDEXING DATE: 199105
ISSN: 0009-921X
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 91130138
CAS REGISTRY/EC NUMBER(S): 0 (Bone Morphogenetic Proteins); 0 (Composite Resins); 0 (Growth Substances); 0 (Hydroxyapatites); 1306-06-5 (Durapatite); 9001-31-4 (Fibrin)

EXHIBIT C-8

List Contains 1 Item.
Current Search Formulation: +HOCKEL M; + 1989 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Angiotropin treatment prevents flap necrosis and enhances dermal regeneration in rabbits.
ARTICLE SOURCE: Arch Surg (United States), Jun 1989, 124(6) p693-8
AUTHOR(S): Hockel M; Burke JF
AUTHOR'S ADDRESS: Universitatsfrauenklinik Mainz, West Germany.
MAJOR SUBJECT HEADING(S): Angiogenesis Factor [pharmacology]; Growth Substances [pharmacology]; Necrosis [prevention & control]; Skin [pathology]; Surgical Flaps
MINOR SUBJECT HEADING(S): Angiogenesis Factor [administration & dosage]; Graft Survival; Injections, Intradermal; Rabbits; Skin [blood supply]; Wound Healing
INDEXING CHECK TAG(S): Animal; Female; Male
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Angiotropin is a potent angiogenesis factor isolated from the serum-free media of cultured, lectin-activated peripheral monocytes. In vitro, the purified substance stimulates migration, phenotypic differentiation, and tube formation, but not proliferation of capillary endothelial cells. When injected intradermally, angiotropin induces, in dose-dependent fashion, angiogenesis associated with skin hyperplasia. We have developed a flap model with insufficient blood supply and a model for contraction-free defect healing in rabbit skin. We show that (1) local pretreatment with angiotropin can prevent flap necrosis and (2) dermal regeneration after wounding can be augmented by angiotropin. From these results, we conclude that angiotropin might be of use as an adjuvant to healing in surgery.
MEDLINE INDEXING DATE: 198909
ISSN: 0004-0010
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 89272615
CAS REGISTRY/EC NUMBER(S): 0 (Angiogenesis Factor); 0 (Growth Substances)

EXHIBIT C-9

List Contains 1 Item.
Current Search Formulation: +KHOURI RK; + 1991 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Tissue transformation into bone in vivo. A potential practical application.
ARTICLE SOURCE: JAMA (United States), Oct 9 1991, 266(14) p1953-5
AUTHOR(S): Khouri RK; Koudsi B; Reddi H
AUTHOR'S ADDRESS: Department of Surgery, Washington University School of Medicine, St Louis, Mo. 63110.
MAJOR SUBJECT HEADING(S): Bone and Bones [physiopathology]; Glycoproteins [administration & dosage]; Growth Substances [administration & dosage]; Muscles [transplantation]; Osteogenesis; Proteins [administration & dosage]
MINOR SUBJECT HEADING(S): Bone Matrix; Bone and Bones [surgery]; Injections; Osteogenesis [drug effects]; Rats, Inbred Lew; Rats; Surgical Flaps; Tissue Transplantation [methods]
INDEXING CHECK TAG(S): Animal; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: The transformation of mesenchymal tissue, such as muscle, into cartilage and bone can be induced by the recently purified osteoinductive factor, osteogenin, and by its parent substratum, demineralized bone matrix. We investigated the possibility of transforming readily available muscle flaps into vascularized bone grafts of various shapes that could be used as skeletal replacement parts. In a rat experimental model, thigh adductor muscle island flaps were placed inside bivalved silicone rubber molds. Prior to closure of the mold, 18 flaps were injected with osteogenin and coated with demineralized bone matrix. Five flaps served as controls and were injected with the vehicle only, and not coated with demineralized bone matrix. The molds were implanted subcutaneously in the rats' flanks and reopened 10 days later. The control flaps consisted of intact muscle without any evidence of tissue transformation, whereas the flaps treated with osteogenin and demineralized bone matrix were entirely transformed into cancellous bone that matched the exact shape of the mold. Using tissue transformation, we were able to generate in vivo, autogenous, well-perfused bones in the shapes of femoral heads and mandibles.
MEDLINE INDEXING DATE: 199112
ISSN: 0098-7484
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 91374707
CAS REGISTRY/EC NUMBER(S): 0 (osteogenin); 0 (osteoinductive factor); 0 (Glycoproteins); 0 (Growth Substances)
GRANT ID NUMBER: 22-3335 44901A

EXHIBIT C-10

National Library of Medicine: IGM Selected Full Records Screen

Selected full citations from 1 MEDLINE records

✔ Related Articles External Links

TITLE: An experimental evaluation of microcapsules for arterial chemoembolization.

AUTHORS: Bechtel W; Wright KC; Wallace S; Mosier B; Mosier D; Mir S; Kudo S

SOURCE: Radiology 1986 Dec;161(3):601-4

CITATION IDS: PMID: 2947261 UI: 87068344

ABSTRACT: Microcapsules, 106 micron (range, 50-350 micron), of different capsular materials (monoglyceride, monodiglyceride, natural wax, cellulose polymer, or lactic acid polymer) with and without floxuridine (2'-deoxy-5-fluorouridine, FUDR) were intraarterially injected into dog kidneys. The drug-release characteristics of the microcapsules, as determined by analysis of renal and systemic venous blood samples over a 6-hour period, were uniphasic or multiphasic depending on the capsular material. Histologic changes of varying degrees were noted in all kidneys embolized except for those subjected to capsules of the cellulose polymer. The most striking changes were produced by the lactide polymer capsules. The potential applications of microencapsuled chemotherapeutic agents in intraarterial transcatheter treatment of cancer are discussed.

MAIN MESH HEADINGS: Antineoplastic Agents/*administration & dosage
*Embolization, Therapeutic

ADDITIONAL MESH HEADINGS: Animal
Antineoplastic Agents/blood
Capsules
Combined Modality Therapy
Dogs
Floxuridine/administration & dosage
Floxuridine/blood
Renal Artery
Support, Non-U.S. Gov't
Support, U.S. Gov't, P.H.S.
1986/12

EXHIBIT C-11

List Contains 1 Item.
Current Search Formulation: +SPRECHER DL; + 1989 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Histopathologic examination of material from angioplasty balloon catheters used in vivo in human coronary arteries.
ARTICLE SOURCE: Atherosclerosis (Netherlands), Feb 1989, 75(2-3) p237-44
AUTHOR(S): Sprecher DL; Mikat EM; Stack R; Sutherland K; Schneider J; Bashore T; Hackel DB
AUTHOR'S ADDRESS: University of Cincinnati Medical Center, Department of Pathology, OH 45267-0529.
MAJOR SUBJECT HEADING(S): Angioplasty, Balloon; Arteriosclerosis [pathology]; Atherosclerosis [pathology]; Coronary Vessels [pathology]; Specimen Handling [methods]
MINOR SUBJECT HEADING(S): Adult; Aged; Angina Pectoris [therapy]; Coronary Vessels [cytology]; Middle Age; Myocardial Infarction [therapy]
INDEXING CHECK TAG(S): Female; Human; Male; Support, U.S. Gov't, P.H.S.
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Reports on vascular pathology post-PTCA in both human and animal coronary vessels have revealed medial and intimal cracks and tears, thrombus formation, platelet accumulation, and loss of endothelial cells. The extent and type of damage can currently be assessed in vivo at the macro level by means of coronary artery angiography. However, this technique cannot define vessel wall characteristics at the cellular level. Our hypothesis is that vessel wall material may adhere to the balloon and thus provide a source for coronary artery cytological investigation in vivo. Ten balloon catheters were evaluated to discern any material which was dislodged from the coronary artery and which remained attached to the balloon catheter or guide wire. Our results indicate that angioplasty catheter balloons frequently have adherent collagen, endothelial cells, organized thrombus, and plaque with obvious cholesterol clefts, that can be retrieved and examined histologically. We conclude that material is often dislodged from the plaque during PTCA. In addition, plaque material removed by the balloon catheter offers an unusual opportunity to analyze the morphologic characteristics of cells from the human coronary artery in vivo.
MEDLINE INDEXING DATE: 198908
ISSN: 0021-9150
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 89228141
GRANT ID NUMBER: HLB 17670

EXHIBIT C-12

List Contains 1 Item.
Current Search Formulation: +JULLIEN P; + 1989 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Acidic cellular environments: activation of latent TGF-beta and sensitization of cellular responses to TGF-beta and EGF.
ARTICLE SOURCE: Int J Cancer (United States), May 15 1989, 43(5) p886-91
AUTHOR(S): Jullien P; Berg TM; Lawrence DA
AUTHOR'S ADDRESS: Unite 532 CNRS, Institut Curie-Biologie, Orsay, France.
MAJOR SUBJECT HEADING(S): Cell Transformation, Neoplastic; Epidermal Growth Factor-Urogastrone [pharmacology]; Transforming Growth Factors [biosynthesis]
MINOR SUBJECT HEADING(S): Agar; Blood; Cell Division [drug effects]; Cell Line; Culture Media; Hydrogen-Ion Concentration; Lactates [pharmacology]; Mice; Transforming Growth Factors [pharmacology]
INDEXING CHECK TAG(S): Animal; Support, Non-U.S. Gov't
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Transient (about 2 hr) acidification to approx. pH 5.0 of agar-gelled overlayers containing untransformed NRK-49F or KiMSV-transformed NRK-49F cells in the presence of fetal calf serum or crude 49F-cell conditioned medium, as sources of latent TGF-beta, elicited EGF-dependent colony formation of 49F cells and inhibited spontaneous growth of transformed cells. Pure, active TGF-beta (porcine, type I) had the same effects on these respective cell types, suggesting that the above results were due to activation of latent TGF-beta in the transiently acidic cellular environment. Similar acidifications in the absence of a source of latent TGF-beta enhanced the positive growth response of 49F and AKR-2B cells to EGF and active TGF-beta and also the negative growth response of KiMSV-transformed 49F cells to active TGF-beta. These results are compatible with the idea that acidic cellular environments, particularly in tumor tissues, are conducive to activation of latent TGF-beta, perhaps in conjunction with other activating mechanisms, and to an enhanced response to some growth factors. However, the heterogeneity of cell populations within tumoral masses presents an obstacle to a clear understanding of the consequences of such activation.
MEDLINE INDEXING DATE: 198908
ISSN: 0020-7136
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 89233486
CAS REGISTRY/EC NUMBER(S): 0 (Culture Media); 0 (Lactates); 50-21-5 (Lactic Acid); 62229-50-9 (Epidermal Growth Factor-Urogastrone); 76057-06-2 (Transforming Growth Factors); 9002-18-0 (Agar)

EXHIBIT C-13

List Contains 1 Item.
Current Search Formulation: +MERRILEES MJ; + 1990 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Endothelial cell stimulation of smooth muscle glycosaminoglycan synthesis can be accounted for by transforming growth factor beta activity.
ARTICLE SOURCE: Atherosclerosis (Netherlands), Apr 1990, 81(3) p255-65
AUTHOR(S): Merrilees MJ; Scott L
AUTHOR'S ADDRESS: Department of Anatomy, School of Medicine, University of Auckland, New Zealand.
MAJOR SUBJECT HEADING(S): Endothelium, Vascular [physiology]; Glycosaminoglycans [biosynthesis]; Muscle, Smooth, Vascular [metabolism]; Transforming Growth Factors [physiology]
MINOR SUBJECT HEADING(S): Cells, Cultured; Endothelium, Vascular [metabolism]; Sulfhydryl Compounds [pharmacology]; Swine; Transforming Growth Factors [metabolism]; Trypsin [pharmacology]
INDEXING CHECK TAG(S): Animal; Support, Non-U.S. Gov't
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Endothelial cell conditioned medium (ECCM) contains a factor which markedly stimulates smooth muscle cell (SMC) glycosaminoglycan (GAG) synthesis. We report here that the factor responsible is transforming growth factor beta (TGF-beta) as assessed by (1) protease and thiol sensitivity, (2) heat and acid enhancement of ECCM activity, and (3) neutralisation of ECCM activity by anti-TGF-beta-immunoglobulin. Anti-TGF-beta-neutralisation was effective against increases in both sulphated and non-sulphated GAG. Previous studies showed that ECCM from EC of varying densities stimulated individual GAG to varying degrees. ECCM from low density EC preferentially stimulated hyaluronic acid (HA) whereas ECCM from intermediate and high density cultures stimulated increasing amounts of sulphated GAG. Exposure of SMC to varying concentrations of TGF-beta produced a similar pattern Exposure of SMC to varying concentrations of TGF-beta produced a similar pattern of response. Very low amounts of TGF-beta (less than 10-500 pg/10 cells) stimulated a marked and significant increase in HA synthesis. Increase in chondroitin sulphate 4/6 was most marked at TGF-beta levels from 500-1000 pg/10(6) cells. At levels above 1000 pg/10(6) cells both HA and sulphated GAG synthesis decreased but still remained elevated above controls. These findings indicate that TGF-beta alone can account for the changes in SMC GAG synthesis stimulated by ECCM. It was also found, however, that heat-treated SMC conditioned medium stimulated SMC GAG synthesis, thus SMC may contribute to the control of their own GAG synthesis through autocrine TGF-beta activity.
MEDLINE INDEXING DATE: 199009
ISSN: 0021-9150
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 90274739
CAS REGISTRY/EC NUMBER(S): EC 3.4.21.4 (Trypsin); 0 (Glycosaminoglycans); 0 (Sulfhydryl Compounds); 76057-06-2 (Transforming Growth Factors)

EXHIBIT C-14

List Contains 1 Item.
Current Search Formulation: +YOUNG SR; + 1990 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Macrophage responsiveness to therapeutic ultrasound.
ARTICLE SOURCE: Ultrasound Med Biol (England), 1990, 16(8) p809-16
AUTHOR(S): Young SR; Dyson M
AUTHOR'S ADDRESS: Department of Anatomy, United Medical School, Guy's Hospital, London, England.
MAJOR SUBJECT HEADING(S): Macrophages [cytology]; Ultrasonic Therapy
MINOR SUBJECT HEADING(S): Cell Count; Cell Division; Cell Line; Cell Survival; Fibroblasts [metabolism]; Growth Substances [biosynthesis]; Macrophages [metabolism]
INDEXING CHECK TAG(S): Animal; Human
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Macrophages are a source of many important growth factors which can act as wound mediators during tissue repair. The aim of this work was to find out if levels of ultrasound which accelerate repair could stimulate the release of fibroblast mitogenic factors from an established macrophage-like cell line (U937). The U937 cells were exposed in vitro to continuous ultrasound at a space average, temporal average intensity of 0.5 W/cm2 at either 0.75 MHz or 3.0 MHz, for 5 min. The macrophage-conditioned medium was removed either 30 min or 12 h after exposure, and placed on 3T3 fibroblast cultures. Fibroblast proliferation (defined here as increase in cell number) was assessed over a 5-day period. The results showed that 0.75 MHz ultrasound appeared to be effective in liberating preformed fibroblast affecting substances from the U937 cells, possibly by producing permeability changes, whereas 3.0 MHz ultrasound appeared to stimulate the cell's ability to synthesize and secrete fibroblast mitogenic factors.
MEDLINE INDEXING DATE: 199109
ISSN: 0301-5629
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 91247100
CAS REGISTRY/EC NUMBER(S): 0 (fibroblast-activating factor); 0 (Growth Substances)

EXHIBIT C-15

List Contains 1 Item.
Current Search Formulation: +SHULTZ PJ; + 1989 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Mitogenic signals for thrombin in mesangial cells: regulation of phospholipase C and PDGF genes.
ARTICLE SOURCE: Am J Physiol (United States), Sep 1989, 257(3 Pt 2) pF366-74
AUTHOR(S): Shultz PJ; Knauss TC; Mene P; Abboud HE
AUTHOR'S ADDRESS: Department of Medicine, Veterans Administration Medical Center, Cleveland, Ohio.
MAJOR SUBJECT HEADING(S): Gene Expression Regulation; Glomerular Mesangium [physiology]; Mitogens [physiology]; Phospholipase C [genetics]; Platelet-Derived Growth Factor [genetics]; Thrombin [physiology]
MINOR SUBJECT HEADING(S): Calcium [metabolism]; Cytosol [metabolism]; Gene Expression Regulation [drug effects]; Glomerular Mesangium [cytology] [metabolism]; Mitogens [pharmacology]; Phosphatidylinositols [metabolism]; Proteins [metabolism]; RNA, Messenger [metabolism]; Thrombin [pharmacology]
INDEXING CHECK TAG(S): Human; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: Thrombin is a proteolytic enzyme of diverse biological activities, which is produced during activation of the coagulation pathway. In addition, thrombin is a mitogen for fibroblasts and endothelial cells. Intraglomerular thrombosis and cell proliferation are common pathological features of several glomerular diseases. We studied the effect of thrombin on deoxyribonucleic acid (DNA) synthesis in cultured human mesangial cells and explored mechanisms of signal transduction involved. Bovine and human thrombin caused dose-dependent increases in DNA synthesis, inositol trisphosphate, and cytosolic calcium [(Ca2+)i]. A threefold increase in inositol-3-trisphosphate (IP3) levels was observed as early as 10 s after the addition of thrombin, whereas increases in (Ca2+)i occurred within 5-10 s and declined rapidly. Stimulation of mesangial cells by thrombin resulted in induction of messenger ribonucleic acids (mRNAs) encoding platelet-derived growth factor (PDGF) A- and B-chains. This was associated with an enhanced secretion of PDGF-like protein. These data provide mechanisms by which thrombin may regulate mesangial cell function in disease states.
MEDLINE INDEXING DATE: 198912
ISSN: 0002-9513
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 89390640
CAS REGISTRY/EC NUMBER(S): EC 3.1.4.3 (Phospholipase C); EC 3.4.21.5 (Thrombin); 0 (Mitogens); 0 (Phosphatidylinositols); 0 (Platelet-Derived Growth Factor); 0 (RNA, Messenger); 7440-70-2 (Calcium)
GRANT ID NUMBER: DK-33665-DK-NIDDK; DK-07470-DK-NIDDK

EXHIBIT C-16

List Contains 1 Item.
Current Search Formulation: "electrical stimulation of growth "; + 1989 - All Articles; + 1990 - All Articles; + 1991 - All Articles; + 1992 - All Articles; + 1993 - All Articles

This Document Selected From: 1989 - 1998 SurgAnLine® [1999 Edition]

ARTICLE TITLE: Weak direct current accelerates split-thickness graft healing on tangentially excised second-degree burns.
ARTICLE SOURCE: J Burn Care Rehabil (United States), Jul-Aug 1991, 12(4) p285-93
AUTHOR(S): Chu CS; McManus AT; Okerberg CV; Mason AD Jr; Pruitt BA Jr
AUTHOR'S ADDRESS: Library Branch, United States Army Institute or Surgical Research, Fort Sam Houston, TX 78234-5012.
MAJOR SUBJECT HEADING(S): Burns [physiopathology]; Electric Stimulation Therapy; Skin Transplantation; Wound Healing [physiology]
MINOR SUBJECT HEADING(S): Burns [pathology] [surgery]; Cell Division; Guinea Pigs; Skin Transplantation [pathology]; Skin [pathology]; Transplantation, Autologous
INDEXING CHECK TAG(S): Animal; Male
PUBLICATION TYPE: JOURNAL ARTICLE
ABSTRACT: We have examined the effects of direct current (DC) conducted through silver-nylon dressings on the healing time and morphologic maturation of split-thickness grafts placed on tangentially excised deep partial-thickness burn wounds. Male guinea pigs (n = 120) were used as the experimental hosts. The DC-treated animals required 2 days for complete revascularization of their grafts; control animals required 7 days (p less than 0.01). The DC-treated animals had increased epithelial proliferation at the graft-wound interface as compared with controls (p less than 0.01). Grafts from DC-treated animals were firmly adherent within 4 days, whereas graft adherence in controls was weak before 7 days after grafting. At 3 months after grafting, control animal grafts had mild contraction with moderate hair loss and thick subepidermal fibrosis; the grafts in DC-treated animals expanded with the growth of the animals and had abundant hair growth and significantly reduced dermal fibrosis (p less than 0.01).
MEDLINE INDEXING DATE: 199202
ISSN: 0273-8481
LANGUAGE: English
UNIQUE NLM IDENTIFIER: 92042249

EXHIBIT C-17